add D3

26. (New) The method of claim 25, wherein the peptide is administered by inhalation.

C' Cont

27. (New) The method of claim 25, wherein the peptide is administered intracerebrally.

add D4

REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following remarks. In the case where the Examiner maintain the rejections over the prior art, alternatively, Applicants petition from Requirement for Restriction with this paper.

I. Status of the Claims

Claims 2, 3, 6-9 and 11-27 are presented. Claims 1, 4, 5 and 10 have been canceled without prejudice or disclaimer. The cancellation of claims made herein does not constitute acquiescence in the propriety of any objection or rejection made by the Examiner, but is made merely to advance the case towards allowance.

Claims 18-27 have been added. Support for the new claims can be found throughout the specification and, especially original claims 1, 4, 5 and 10. Claims 2, 3, 6-9 and 11-17 have been withdrawn from consideration as being directed to a non-elected invention.

II. Election/Restriction

Applicants hereby petition from the restriction requirement, originally set forth in the Office Action mailed September 7, 2000, and made final in the Office Action mailed March 2, 2001.

In the Office Action of September 7, 2000, the Examiner restricted the claims of the present application into nine (9) groups. In the response to the Office Action,

Applicants provisionally elect claims of Group I, claims 1, 4, 5 and 10 drawn to a method for modulating neuronal activity, with traverse based on the unity of invention of claims between Groups I and III. The Examiner, however, has made the restriction requirement final in the instant Office Action, finding that Applicants' arguments are not persuasive.

Applicants respectfully traverse the Examiner's rationale for the reasons discussed below.

As an initial matter, the claims 1, 4, 5, and 10 in the Groups I, have been cancelled, and claims 18, 19, 20, 21, 22, 23, 24, 25, 26, and 27 have been added. Because new claims substantially correspond to the claims of Groups I and III, Applicants believe that our petition from the restriction requirement also apply to these new claims, although the arguments for the petition are presented herein with respect to the original claims of Group I and claims 6 and 9 of Group III.

In the instant Office Action, finding a neuroactive peptide comprising SEQ ID NO:1 as the special technical feature, the Examiner alleges that this special technical feature, that is, is anticipated by prior art and the allowed categories are not inclusive of multiple methods of use of the special technical feature, and thus Applicants' arguments are not persuasive.

Claims 1 and 4 of the Group I, at the time of restriction, read as follows:

1. A method of modulating neuronal activity, comprising the step of administering an effective amount of a neuroactive peptide having at least one of the biological activities of angiotensin IV as herein defined, comprising the amino acid sequence:

Leu-Val-Val-Tyr-Pro-Trp-Thr-Gln-Arg-Phe, (SEQ ID NO: 1); or a biologically-active analogue or fragment of said peptide, to a mammal in need of such treatment.

4. A method according to any one of claim 1, in which the biological activity is selected from the group consisting of modifying learning, modifying behavior, vasoactive effects, dilation of cerebral arteries, increase in renal blood flow, increase in

stereotype behavior, facilitating memory retrieval, neurite modeling and alleviation of the effects of spinal cord injury.

Claims 6 and 9 of the Group III, at the time of restriction, read as follows:

6. A method of treating a condition selected from the group consisting of dementia; Alzheimer's disease; neuro-degenerative disorders of cholinergic pathways and sensory pathways; motor neuron disease; sensory peripheral neuropathies; motor peripheral neuropathies; brain injury and spinal cord injury resulting from trauma, and vascular disease, comprising the step of administering an effective amount of a neuroactive peptide having at least one of the biological activities of angiotensin IV as herein defined, comprising the amino acid sequence:

Leu-Val-Val-Tyr-Pro-Trp-Thr-Gln-Arg-Phe, (SEQ ID NO: 1); or a biologically-active analogue or fragment of said peptide, to a mammal in need of such treatment.

9. A method according to claim 6, in which the biological activity is selected from the group consisting of modifying learning, modifying behavior, vasoactive effects, dilation of cerebral arteries, increase in renal blood flow, increase in stereotype behavior, facilitating memory retrieval, neurite modeling and alleviation of the effects of spinal cord injury.

Direct comparison of claim languages of claims 1 and 6 clearly shows that both methods are based on the "use of neuroactive peptides recited in the claims in a mammal in need of such treatment, modulating neuronal activity," which should be recognized as the special technical feature of these claims. According to the Office Action of September 7, 2000, the Examiner stated that claims 1, 4, 5 and 10 in Group I were drawn to **first technical feature** and first method of use of a neuroactive peptide, namely, the modulation of neuronal activity, and that claims 6 and 9 of Group III were drawn to the second method, that is, treatment using **first technical feature**. With the above indication, the Examiner also appeared to understand that first technical feature was the use of a neuroactive peptide for modulating neuronal activity, not a neuroactive peptide itself.

Thus, Applicants respectfully submit that the lack of novelty of the neuroactive peptide recited in the claims is not relevant to determine the unity of invention of this case.

Existence of the special technical feature common to claims of Groups I and III is again confirmed from the Examiner's own observation made in requirement of election of species. More specifically, the Examiner identified species of Groups I and III as follows: [stated in the Office Action of September 7, 2000 that the application contained claims directed to more than one species of generic invention. These species were deemed to lack unity of invention because they were not so linked as to form a single general inventive concept under CFR Rule 13.1.

The species identified by the Examiner were as follows:]

In GROUP I, species of biological activity are selected from the group consisting of:

A) **modifying learning and facilitating memory retrieval**
B) **modifying behavior and increase in stereotypy behavior**
C) **vasoactive effects, dilation of cerebral arteries, and increase in renal blood flow**
D) **neurite modeling**
E) **alleviation of effects of spinal cord injury**
F) motor neuron activity and
H) neuronal development.

In GROUP III, species of conditions were selected from the group consisting of:

A) dementia
B) Alzheimer's disease
C) neuro-degenerative disorders of cholinergic pathways and sensory peripheral neuropathies
D) brain injury
G) spinal cord injury resulting from trauma
H) spinal cord injury resulting from hypoxia, spinal cord injury resulting from vascular disease and **alleviation of the effects of spinal cord injury**

I) **modifying memory and facilitating memory retrieval**
J) **modifying behavior and increase in stereotypy behavior**
K) **vasoactive effects, dilation of cerebral arteries, and increase in renal blood flow**
L) **neurite modeling.**

Although the species of Groups I and III are designated by the Examiner as "biological activity" and "conditions," respectively, comparison of individual species shows that there exists species common to both biological activity and conditions. Thus, these common species between biological activity and conditions again evidence the special technical feature common between claims of Groups I and III, and lead to the conclusion that Groups are so linked as to form a "single general inventive concept," use of the neuroactive peptide for modulating neuronal activity. In other words, claims of Groups I and III are linked such that conditions listed in claim 6 of Group III result from the biological activities recited in claims of Group I.

Such relationship is further confirmed from the claim language found in claims 1 and 6. Both claims 1 and 6 refer to "administering a neuroactive peptide . . . to a mammal in need such treatment." The term, "a mammal in need such treatment" refers to a mammal requiring modulation of neuronal activity, encompassing a mammal which has conditions listed in claim 6. Thus, the common subject to which these methods apply is another clear indication of the link between the biological activities modulated by the peptide comprising SEQ ID NO: 1, and the conditions treated in the claims in Group III. The biological activities listed in new claim 18, belonging to Group I, are likely to be involved in several of the conditions treated in Group III.

Thus, Applicants respectfully submit that there exists a special technical feature common to all of the claims of Groups I and III, which is the "use of the recited neuroactive peptide for modulating neuronal activity." None of the prior art references discloses the use of the neuroactive peptide for modulating neuronal activity, which is further explained below with respect to the anticipation rejection.

In addition, because claims of Groups I and III are linked each other by the special technical feature as set forth above, these claims should be considered a single method, rather than multiple methods.

Moreover, the fact remains that there is no serious burden to search and examine Groups I and III together. There is no indication in either Office Action, these methods fall within different categories of classification. As demonstrated above, Groups I and III share the same special technical feature, thus, it would not be an undue burden to search Groups I and III together unless the Examiner can provide evidence otherwise.

Therefore, it is respectfully requested that the requirement for restriction between claims of Groups I and III in this case be withdrawn. If the Examiner maintains the restriction requirement, please treat this paper as a petition from the restriction requirement.

III. Rejection based on 35 USC §112, second paragraph

The Examiner has rejected claims 1, 4, 5 and 10 under 35 USC §112, second paragraph as allegedly indefinite. Specifically, the Examiner has objected to the recitation of "an effective amount of a neuroactive peptide having at least one of the biological activities of angiotensin IV as defined herein" because it lacks proper antecedent basis. Applicants respectfully traverse this rejection.

At the outset, Applicants note that claims 1, 4, 5 and 10 have been cancelled and claim 18, added herein, defines biological activity as one selected from the group consisting of modifying learning, modifying behavior, vasoactive effects, dilation of cerebral arteries, increase in renal blood flow, increase in stereotype behavior, facilitating memory retrieval, neurite modeling and alleviation of the effects of spinal cord injury. Thus, Applicants respectfully submit that new claim 18 clearly referring to the specific biological activity of neuroactive peptide renders this rejection moot. Accordingly, withdrawal of the rejection is respectfully requested.

IV. ***Rejection based on 35 USC § 102(b) or § 102(e)***

The Examiner has rejected claims 1, 4, 5 and 10 under 35 USC § 102(a) or 102(e) as anticipated by US Patent No. 5,599,907 to Anderson *et al.* ("Anderson") or US Patent 5,861,483 to Wolpe *et al.* ("Wolpe"). The Examiner has rejected claims 1, 4, 5 and 10 under 35 USC § 102(b) as anticipated by US Patent No. 5,063,206 to Bridge *et al.* ("Bridge"). Applicants respectfully traverse and address these rejections and the cited references to the extent they apply to the claims 18-27, as added herein.

The Examiner asserts that due to the failure of specifying a required effect of administration of SEQ ID NO: 1 in claims 1, 4, 5 and 10, biological activity of peptides disclosed in Anderson or Wolpe constitutes at least one of the biological activities of angiotensin IV and inherently comprises biological activities enumerated in claim 4.

As an initial matter, Applicants note that claims 1, 4, 5 and 10 have been cancelled and new claim 18 specifically recites biological activities modulated by the prescribed neuroactive peptide, resulting in modulating neuronal activity. None of the cited references teaches or suggests that peptides disclosed therein can modulate the biological activities recited in claim 18, resulting in modulating neuronal activity.

Anderson discloses multimeric hemoglobin-like proteins, more specifically, control of multimer formation within hemoglobin-like proteins to facilitate the purification and characterization of such proteins. Anderson further discloses use of multimeric hemoglobin-like proteins for supplementing the oxygen carrying capacity of blood.

Wolpe relates to the use of polypeptide inhibitors of stem cell proliferation ('INPROL') including peptides of SEQ ID NO: 4 and 26, that share 100% identity with peptide of SEQ ID NO: 1 in the present application. Wolpe teaches the use of INPROL to treat humans or animals having autoimmune diseases, aging, cancer, myelodysplasia, preleukemia, leukemia, psoriasis or other diseases involving hyper-proliferative conditions. Wolpe relates to end-stage stem cells that are short-lived and must be replaced continuously throughout life. Wolpe provides examples of haematopoetic stem cells that

include cells from the bone marrow, umbilical cord blood, or peripheral blood and other cells that are necessary for the production of mature blood cells.

However, neither Anderson nor Wolpe teaches or suggests that the protein or polypeptide disclosed therein can be used for modulating neuronal activity, let alone specific biological activities recited in claims 18.

To make up for the lack of disclosure, the Examiner asserts that supplementing oxygen carrying capacity of blood or properties of inhibiting stem cell proliferation constitutes at least one of the biological activities of angiotensin IV, and inherently comprises modification of learning, facilitating memory retrieval and vasoactive effects including dilation of cerebral arteries and increasing blood flow.

First of all, new claim 18 incorporating specific biological activities modulated by the neuroactive peptide prescribed in claim 18 clearly shows that the method of claim 18 does not encompass oxygen carrying capacity of blood as the biological activities. More importantly, contrary to the Examiner's assertion, neither supplementing oxygen carrying capacity nor inhibiting stem cell proliferation qualifies as inherent disclosure of the specific biological activities in claim 18. Supplementing oxygen carrying capacity is based on a general property of hemoglobin-like proteins carrying oxygen. Cell division characteristics of cells associated with modulation of neuronal activity are known to be very different from that of the highly proliferative nature of the stem cells disclosed in Wolpe. Indeed, stem cells referred to in Wolpe are undifferentiated cells whereas the cells that modulate neuronal activity are differentiated cells.

Thus, a person of ordinary skill would not recognize that supplementing oxygen carrying capacity or inhibiting stem cell proliferation affects biological activities as specified in claim 18, thereby resulting in modulating neuronal activity.

In relying upon the theory of inherency the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). Applicants

respectfully submit that the Examiner fails to meet such burden in this case. The Examiner has not provide any basis or technical reasoning how modulating the specified biological activities of the recited neuroactive peptide necessarily flows from the teachings of Anderson or Wolpe that their peptide can be used to supplement oxygen carrying capacity of blood or to inhibit stem cell proliferation. The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert,* 9 F.3d 1531, 1534 (Fed. Cir. 1993). Also, inherency may not be established by probabilities or possibilities. *In re Robertson,* 169 F.3d 743, 745 (Fed. Cir. 1999).

Thus, given the lack of disclosure in Anderson or Wolpe, combined with the absence of any other objective evidence showing missing description, a person of ordinary skill in the art would not infer from Anderson or Wolpe that specific biological activities modulated by the recited neuroactive peptide in claim 18 are inherently present in properties of peptides disclosed in the prior.

It is axiomatic that, for a reference to be anticipatory, it must describe each and every element of the claimed invention. However, neither Anderson nor Wolpe, explicitly or inherently, teaches or suggests any one of biological activities the recited peptides of claim 18. Accordingly, none of the cited references discloses each and every element of the claimed invention either explicitly or inherently.

Bridge teaches the use of peptides that inhibit the binding of human immunodeficiency virus (HIV) to receptor sites on the cell surface to treat psoriasis and neuropsychiatric disorders. None of the peptide sequences reported in Bridge are identical to the peptide sequence of claim 18. Therefore, due to the failure of teaching of the full amino acid sequence of SEQ ID NO: 1, Bridge does not qualify as an anticipatory reference.

Accordingly, withdrawal of all of the anticipation rejections is respectfully requested.

In view of the foregoing amendments and remarks, applicants respectfully request favorable reconsideration and allowance of the pending claims. If there are any issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is hereby respectfully invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

Date: 2 August 2001

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